

# Essential Nutrient Interactions: Does Low or Suboptimal Magnesium Status Interact with Vitamin D and/or Calcium Status?<sup>1,2</sup>

Andrea Rosanoff,<sup>3\*</sup> Qi Dai,<sup>4</sup> and Sue A Shapses<sup>5</sup>

<sup>3</sup>Center for Magnesium Education and Research, Pahoa, HI; <sup>4</sup>Vanderbilt Epidemiology Center, Department of Medicine, School of Medicine, Vanderbilt University, Nashville, TN; and <sup>5</sup>Rutgers University, New Brunswick, NJ

## ABSTRACT

Although much is known about magnesium, its interactions with calcium and vitamin D are less well studied. Magnesium intake is low in populations who consume modern processed-food diets. Low magnesium intake is associated with chronic diseases of global concern [e.g., cardiovascular disease (CVD), type 2 diabetes, metabolic syndrome, and skeletal disorders], as is low vitamin D status. No simple, reliable biomarker for whole-body magnesium status is currently available, which makes clinical assessment and interpretation of human magnesium research difficult. Between 1977 and 2012, US calcium intakes increased at a rate 2–2.5 times that of magnesium intakes, resulting in a dietary calcium to magnesium intake ratio of >3.0. Calcium to magnesium ratios <1.7 and >2.8 can be detrimental, and optimal ratios may be ~2.0. Background calcium to magnesium ratios can affect studies of either mineral alone. For example, US studies (background Ca:Mg >3.0) showed benefits of high dietary or supplemental magnesium for CVD, whereas similar Chinese studies (background Ca:Mg <1.7) showed increased risks of CVD. Oral vitamin D is widely recommended in US age-sex groups with low dietary magnesium. Magnesium is a cofactor for vitamin D biosynthesis, transport, and activation; and vitamin D and magnesium studies both showed associations with several of the same chronic diseases. Research on possible magnesium and vitamin D interactions in these human diseases is currently rare. Increasing calcium to magnesium intake ratios, coupled with calcium and vitamin D supplementation coincident with suboptimal magnesium intakes, may have unknown health implications. Interactions of low magnesium status with calcium and vitamin D, especially during supplementation, require further study. *Adv Nutr* 2016;7:25–43.

**Keywords:** magnesium, calcium, vitamin D, calcium/magnesium ratio, nutrient interactions, essential mineral interactions

## Introduction

The role of magnesium in health physiology and metabolism has been well studied; however, its interactions with calcium and vitamin D, especially when magnesium is inadequate, are less well known. This lack of data is in contrast with the extensive literature on interactions of vitamin D with calcium. This article reviews general intakes of and assessment issues for dietary magnesium and explores interactions of magnesium with the nutrients calcium and vitamin D.

## Magnesium

### Health effects of inadequate magnesium intake

Magnesium status is low in populations who consume modern processed-food diets that are high in refined grains, fats,

and sugars (1). Low magnesium status may lead to chronic diseases (**Table 1**) (2–36). For example, studies have linked low magnesium status to a greater risk of metabolic syndrome (MetS)<sup>6</sup> (24, 27–31), type 2 diabetes (T2D) (17, 37, 38), cardiovascular disease (CVD) (7, 8, 39), skeletal disorders (32, 34, 36, 40–42), chronic obstructive pulmonary disease (43–47), and possibly some cancers (48–51). Low magnesium status has also been associated with depression (52–55) and decreased cognition (56, 57). These diseases have large human and financial costs, as reported in the Global Burden of Disease Study (58). Therefore, there is a need to explore the consequences of suboptimal magnesium status in populations consuming modern processed-food diets.

<sup>1</sup> Supported by NIH grants R01CA149633 and U01CA182364 (to QD) and AG12161 (to SAS). This is a free access article, distributed under terms (<http://www.nutrition.org/publications/guidelines-and-policies/license/>) that permit unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

<sup>2</sup> Author disclosures: A Rosanoff, Q Dai, and SA Shapses, no conflicts of interest.

\*To whom correspondence should be addressed. E-mail: arosanoff@gmail.com.

<sup>6</sup> Abbreviations used: BMD, bone mineral density; CLMD, chronic latent magnesium deficit; CVD, cardiovascular disease; IHD, ischemic heart disease; MetS, metabolic syndrome; PTH, parathyroid hormone; T2D, type 2 diabetes; *TRPM7*, transient receptor potential melastatin 7; VDBP, vitamin D binding protein; 1,25(OH)<sub>2</sub>D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

**TABLE 1** Studies of magnesium status, categorized by health outcome and type of study<sup>1</sup>

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
CVD					
Joosten et al. 2013 (2)	Cohort	Men and women free of known CVD	Urinary Mg as an indicator of dietary Mg uptake; lowest quintile urinary Mg (men <2.93 mmol/d, women <2.45 mmol/d) vs. upper 4 quintiles; plasma Mg; followed 10 y.	Risk of fatal and non-fatal IHD	Urinary Mg: lowest quintile vs. upper 4 quintiles: HR of 1.60 (95% CI: 1.28, 2.00) Circulating Mg: no association with IHD
Khan et al. 2013 (3)	Cohort	Men and women from the Framingham Offspring Study free of CVD and AF	Serum Mg ≤0.73 mmol/L vs. serum Mg >0.73 mmol/L; followed up to 20 y	AF incidents	HR of 1.52 (95% CI: 1.00, 2.31) with hypomagnesemia (serum Mg ≤0.73 mmol/L)
Misialek et al. 2013 (4)	Cohort	Men and women free of AF in the ARIC study	Quintiles of dietary and serum Mg (middle serum Mg quintile ≥0.80–0.83 mmol/L)	AF risk	Dietary Mg: no association observed with AF Circulating Mg: lowest serum Mg quintile compared with middle quintile (HR: 1.34; 95% CI: 1.16, 1.54); other serum Mg quintiles compared with middle quintile: no difference
Del Gobbo et al. 2012 (5)	Cross-sectional	Cree adults (>18 y)	Hypomagnesemia (≤0.7 mmol/L) vs. normomagnesemia (>0.7 mmol/L)	Prevalence of PVC	PVC: 50% and 20% in hypomagnesemic and normomagnesemic individuals, respectively (P = 0.015)
Larsson et al. 2012 (6)	Meta-analysis of cohort studies	7 Prospective studies	Dose-response meta-analysis of Mg intake	Risk of stroke	Increasing dietary Mg: total risk of stroke: RR of 0.92 (95% CI: 0.88, 0.97); ischemic stroke: RR of 0.91 (95% CI: 0.87, 0.96); intracerebral hemorrhage: RR of 0.96 (95% CI: 0.84, 1.00); subarachnoid hemorrhage: RR of 1.01 (95% CI: 0.90, 1.14)
Del Gobbo et al. 2013 (7)	Meta-analysis of cohort studies	16 Studies	Circulating Mg: per 0.2 mmol/L; dietary Mg: per 200 mg/d	Incidence of CVD	Circulating Mg: lower risk of CVD (RR: 0.70; 95% CI: 0.56, 0.88 per 0.2 mmol/L) and IHD (RR: 0.83; 95% CI: 0.75, 1.05) Dietary Mg: not significant for CVD (RR: 0.89; 95% CI: 0.75, 1.05); 22% lower risk of IHD (RR: 0.78; 95% CI: 0.67, 0.92)

(Continued)

**TABLE 1** (Continued)

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
Qu et al. 2013 (8)	Meta-analysis of cohort studies	19 Studies	High vs. low dietary Mg intake and serum Mg concentrations	Total CVD events	Dietary Mg: RR of 0.85 (95% CI: 0.78, 0.92) for high vs. low Mg intake; Mg intake shows significant nonlinear association with risk of CVD events Circulating Mg: RR of 0.77 (95% CI: 0.66, 0.87) for high vs. low; only serum Mg concentrations of 0.72–0.9 mmol/L were significantly associated with total CVD event risk
Nie et al. 2013 (9)	Meta-analysis of cohort studies	8 Studies of stroke cases	Dietary Mg intake; high vs. low intake plus dose-response analysis	Risk of stroke incidence or stroke mortality	Highest vs. lowest dietary Mg: risk of total stroke: RR of 0.89 (95% CI: 0.82, 0.97); risk of ischemic stroke: RR of 0.88 (95% CI: 0.80, 0.98); dose-response analysis showed a borderline inverse association between Mg intake and total stroke risk (increment of 100 mg/d), with RR of 0.98 (95% CI: 0.95, 1.0)
Alghamdi et al. 2005 (10)	Meta-analysis of randomized clinical trials	8 Trials of post-coronary artery by-pass surgery patients	Intravenous Mg vs. no intravenous Mg	Incidence of postoperative AF	With intravenous Mg: RR of 0.64 (95% CI: 0.47, 0.97)
Shiga et al. 2004 (11)	Meta-analysis of randomized clinical trials	17 Trials in post-cardiac surgery patients	Mg supplementation vs. no supplementation	Incidence of arrhythmias	With Mg supplementation: RR of 0.77 (95% CI: 0.63, 0.93) for supraventricular arrhythmias; RR of 0.52 (95% CI: 0.31, 0.87) for ventricular arrhythmias; no effect on incidence of perioperative myocardial infarction or mortality
CVD mortality Reffellmann et al. 2011 (12)	Cohort	Subjects not receiving Mg supplementation	Serum Mg ≤0.73 mmol/L vs. >0.73 mmol/L; follow-up 10.1 y	CVD mortality	Serum Mg ≤0.73 mmol/L: 3.44 deaths/1000 person-years; serum Mg >0.73 mmol/L: 1.53 deaths/1000 person-years

(Continued)

**TABLE 1** (Continued)

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
Chiuvè et al. 2013 (13)	Cohort	Women free of disease	Dietary and plasma Mg quintiles	Risk of fatal IHD	Dietary Mg: comparing high with low quintiles: RR of 0.61 (95% CI: 0.45, 0.84) Circulating Mg: plasma Mg concentrations >2.0 mg/dL were associated with lower risk but were not significant (RR: 0.67; 95% CI: 0.44, 1.04)
Del Gobbo et al. 2013 (7)	Meta-analysis of cohort studies	16 Studies	Circulating Mg: per 0.2 mmol/L; dietary Mg: per 200 mg/d	Fatal IHD	Dietary Mg: nonlinear association ( $P < 0.001$ ) with inverse association at intakes >250 mg/d; RR of 0.73 (95% CI: 0.62, 0.86 for >250 mg/d vs. <250 mg/d) Circulating Mg: RR of 0.61 (95% CI: 0.37, 1.00)
Joosten et al. 2013 (2)	Cohort	Men and women free of known CVD	Urinary excretion as an indication of intestinal Mg absorption, and plasma Mg followed 10 y	IHD mortality	Urinary Mg: lowest quintile compared with upper 4 quintiles: 1.70 (95% CI: 1.10, 2.61) Circulating Mg: no association with fatal IHD
All-cause mortality Reffelmann et al. 2011 (12)	Cohort	Subjects not receiving Mg Supplementation	Serum Mg $\leq 0.73$ mmol/L vs. $>0.73$ mmol/L; follow-up 10.1 y	All-cause mortality	Serum Mg $\leq 0.73$ mmol/L: 10.95 deaths/1000 person-years; serum Mg $>0.73$ mmol/L: 1.45 deaths/1000 person-years
Booth et al. 2003 (14)	Cohort	Patients undergoing 20% CABG surgery	Low Mg defined as serum Mg $<1.8$ mmol/L at any point within 8 d after surgery	Death at 1 y after surgery	HR of 2.0 (95% CI: 1.19, 3.37) if defined low-serum Mg occurred
Ishimura et al. 2007 (15)	Cohort	Patients receiving maintenance hemodialysis	Baseline serum (baseline Mg $\leq 1.14$ mmol/L vs. Mg $>1.14$ mmol/L) followed for 51 mo	All-cause mortality	Low circulating Mg: HR of 0.485 (95% CI: 0.241, 0.975); evidence of a "J curve"
Singhi et al. 2003 (16)	Cohort	Children in a PICU (6 mo–12 y)	Hypomagnesemic vs. normomagnesemic	Percentage of mortality	Hypomagnesemic: 30%; normomagnesemic: 3.3%
T2D Dong et al. 2011 (17)	Meta-analysis of 13 cohort studies	Men and women	Mg intake	Risk of T2D	Inverse risk of T2D with Mg intake: RR of 0.78 (95% CI: 0.73, 0.84)
Larsson and Wolk, 2007 (18)	Meta-analysis of 7 cohort studies	Men and women	Mg intake, food and supplements	Relative risk of T2D	Overall RR of 0.85 (95% CI: 0.79, 0.92) for 100 mg/d increase in dietary Mg

(Continued)

**TABLE 1** (Continued)

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
Sales et al. 2011 (19)	Cross-sectional	T2D patients	Measured Mg intake plus urinary, plasma, and RBC Mg	Fasting glucose, 2-h postprandial glucose, and HbA1c	In T2D patients, 77% had $\geq 1$ Mg status measure below cut-off; all mean Mg measures were low: dietary Mg ( $228 \pm 43$ mg Mg/d), urinary Mg ( $2.8 \pm 1.51$ mmol/d), plasma Mg ( $0.71 \pm 0.08$ mmol/L), and RBC Mg ( $1.92 \pm 0.23$ mmol/L); poor blood glucose control: fasting glucose ( $8.1 \pm 3.7$ mmol/L), 2-h postprandial glucose ( $11.1 \pm 5.1$ mmol/L), HbA1c ( $11.4\% \pm 3.0\%$ )
Agrawal et al. 2011 (20)	Cross-sectional	60 Healthy controls; study groups: 30 individuals with diabetes with no complications; 60 with diabetes plus macrovascular complications	Serum Mg	Fasting glucose, HbA1c, and serum Mg	Fasting glucose and HbA1c was higher in study groups vs. healthy controls Circulating Mg: low serum Mg concentrations in study groups with diabetes compared with the healthy control group ( $P < 0.05$ ); study groups with macrovascular complications showed significant correlation between serum Mg and fasting glucose and HbA1c
Sharma et al. 2007 (21)	Cross-sectional	50 Participants with diabetes (types 1 and 2) vs. 40 healthy controls	Serum Mg	Participants with diabetes vs. healthy controls	Serum Mg lower in diabetics than in healthy individuals ( $P < 0.005$ ); lower in participants with diabetes with complications than in those without complications ( $P < 0.001$ ); duration of diabetes inversely related to serum Mg
Chambers et al. 2006 (22)	Cross-sectional	African-American and Hispanic adults (US), aged $53 \pm 16$ y	Serum Mg	Participants with diabetes vs. normal fasting glucose	Serum Mg of $0.80 \pm 0.07$ mmol/L in participants with diabetes and $0.84 \pm 0.07$ mmol/L in those with normal fasting glucose ( $P < 0.001$ )

(Continued)

**TABLE 1** (Continued)

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
Saggese et al. 1991 (23)	RCT	Children with diabetes (9.4 ± 2.5 y), with age- and sex-matched controls	Oral Mg therapy 6 mg · kg <sup>-1</sup> · d <sup>-1</sup> for 60 d	Serum Mg, total and ionized serum Ca, intact PTH, calcitriol, osteocalcin	Circulating Mg: serum Mg lower in children with diabetes than controls at baseline; with supplementation, serum Mg significantly increased, reaching levels of age- and sex-matched control values
Solati et al. 2014 (24)	RCT	Patients with T2D	Oral Mg 300 mg/d for 3 mo	Fasting blood and 2-h postprandial glucose vs. control	Oral Mg lowered fasting blood glucose ( <i>P</i> < 0.0001) and 2-h postprandial glucose ( <i>P</i> < 0.01)
Song et al. 2006 (25)	Meta-analysis of 9 randomized clinical trials	Patients with T2D	Oral Mg median dose = 360 mg/d	Fasting glucose in treatment vs. control groups	Oral Mg compared with placebo lowered fasting glucose (−0.56 mmol; 95% CI: −1.10, −0.01) but not HbA1c (−0.31%; 95% CI: −0.81, 0.19)
Yang et al. 1999 (26)	Case-control	Death from diabetes vs. other causes in Taiwan	Drinking water Mg concentrations	Deaths from diabetes and Mg concentration in drinking water	Protective effect of Mg intake from drinking water
MetS He et al. 2006 (27)	Cohort	Healthy Americans aged 18–30 y, followed 15 y	Dietary Mg intake quartiles, highest vs. lowest	Development of MetS	Dietary Mg, high vs. low quartile: HR of 0.69 (95% CI: 0.52, 0.91)
Huang et al. 2012 (28)	Cross-sectional	Elderly patients with T2D; some with depression	Mg intake quartiles	Depression and variables of MetS	MetS and depression both associated with lower Mg intake ( <i>P</i> < 0.05); positive association between Mg intake and HDL cholesterol ( <i>P</i> < 0.005); inverse association between Mg intake and TGs, waist circumference, % body fat, and BMI ( <i>P</i> < 0.005); 88.6% had Mg intakes <DRI; 37% had hypomagnesemia
Guerrero-Romero and Rodríguez-Moran, 2002 (29)	Cross-sectional	192 Individuals with MetS and 384 age- and sex-matched healthy controls	Compared serum Mg of MetS subjects vs. healthy controls	Risk of MetS with low serum Mg	Low serum Mg increased risk of MetS (OR: 6.8; 95% CI: 4.2, 10.9); low serum Mg found in 65.6% of patients with MetS and in 4.8% in healthy controls ( <i>P</i> < 0.00001)

(Continued)

**TABLE 1** (Continued)

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
Solati et al. 2014 (24)	RCT	T2D patients	300 mg Mg/d or placebo for 3 mo	Variables of MetS	Oral Mg improved lipid profile, blood pressure, and hepatic enzymes in addition to significantly lowering fasting ( $P < 0.0001$ ) and postprandial ( $P < 0.01$ ) glucose
Rodríguez-Moran et al. 2014 (30)	RCT	Metabolically obese normal-weight people with hypomagnesemia	382 mg Mg/d vs. placebo for 4 mo	Change in HOMA-IR index, fasting glucose and TG concentrations, BP	Oral Mg improved all MetS variables: HOMA-IR: -46.5% for Mg vs. -5.4% for placebo ( $P < 0.0001$ ); fasting glucose: -12.3% for Mg vs. -1.8% for placebo ( $P < 0.05$ ); TGs: -47.4% for Mg vs. -10.1% for placebo ( $P < 0.0001$ ); SBP: -2.1% for Mg vs. 3.9% for PI ( $P < 0.05$ ). +3.9% for placebo ( $P < 0.05$ ); DBP: -3.8% for Mg vs. +7.5% for placebo ( $P < 0.05$ )
Dibaba et al. 2014 (31)	Meta-analysis	6 Cross-sectional studies	Compared lowest with highest dietary Mg intake groups	Risk of MetS	Lower Mg intakes had risk of MetS: OR of 0.69 (95% CI: 0.59, 0.81)
Skeletal disorders Tucker et al. 1999 (32)	Cohort	Elderly subjects, Framingham Heart Study	Dietary Mg intakes including supplements	4-y Change in BMD (3 hip sites, 1 forearm site)	Mg intake was associated with less BMD decline at 2 hip sites; greater BMD at 1 hip site for both men and women; greater BMD in forearm for men
Orchard et al. 2014 (33)	Cohort	Postmenopausal women (Women's Health Initiative Observational Study)	High vs. low total dietary Mg intake quintile (quintile 5 >422.5 mg/d vs. quintile 1 <206.5 mg/d)	Hip fractures and whole-body BMD	High- vs. low-Mg group: hip BMD: 3% higher in high- vs. low-Mg group ( $P < 0.001$ ); whole-body BMD: 2% higher ( $P < 0.001$ ); incidence and RR of hip fractures: no change across dietary Mg quintiles; risk of lower arm or wrist fractures increased at quintiles 4 (HR: 1.15; 95% CI: 1.01, 1.32) and 5 (HR: 1.23; 95% CI: 1.07, 1.42); women in the higher quintiles more physically active, at increased risk of falls

(Continued)

**TABLE 1** (Continued)

Authors, year (ref)	Study design	Population	Magnesium exposure measurement and approach	Outcome endpoint	Outcome measure
Ryder et al. 2005 (34)	Cross-sectional	White and black older men and women aged 70–79 y	Dietary Mg quintiles	BMD	BMD in white women: 0.04 g/cm <sup>2</sup> higher in high ( $P = 0.05$ ) vs. low quintile of dietary Mg; in white men: 0.02 g/cm <sup>2</sup> ( $P = 0.005$ ); higher whole-body BMD associated with Mg intake for white men ( $P < 0.05$ ) and white women ( $P < 0.005$ ) but no such association in black men and women
New et al. 2000 (35)	Cross-sectional	62 Healthy women aged 45–55 y	Mg intake from FFQ	Total bone mass	Dietary Mg intake associated with higher total bone mass: significant Pearson correlation ( $P < 0.05$ to $P < 0.005$ )
Stendig-Lindberg et al. 1993 (36)	Clinical study	54 Postmenopausal women with osteoporosis	31 Received oral Mg therapy for 2 y; 23 without treatment served as controls	Mean bone density	71% of Mg group responded by a 1%–8% increase in bone density, with increases at both 1 and 2 y; mean bone density of all Mg therapy patients increased after 1 y ( $P < 0.02$ ) and remained unchanged at 2 y ( $P < 0.05$ ), whereas mean bone density decreased in untreated controls ( $P < 0.001$ )

<sup>1</sup> AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMD, bone mineral density; BP, blood pressure; CABG, coronary artery by-pass grafting; ISD, ischemic heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; IHD, ischemic heart disease; MetS, metabolic syndrome; PICU, pediatric intensive care unit; PTH, parathyroid hormone; PVC, premature ventricular complex; RCT, randomized controlled trial; ref, reference; SBP, systolic blood pressure; T2D, type 2 diabetes.

### Low magnesium dietary intakes in the United States

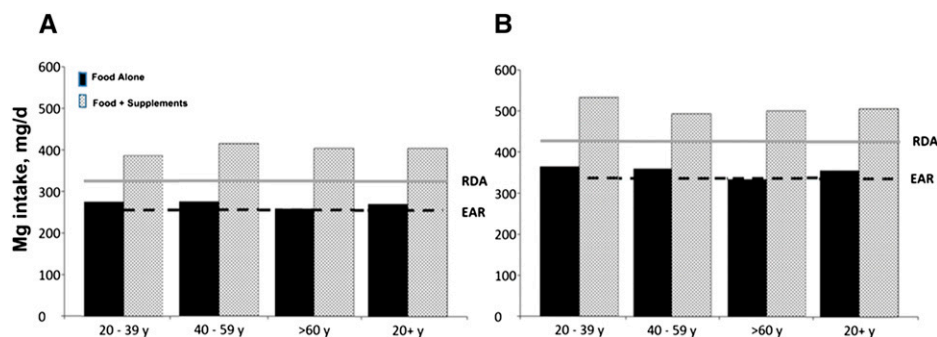
In a 2011–2012 USDA survey of the latest data available for US dietary intake amounts, mean magnesium intakes for adults were below the RDA (Figure 1) (59, 60). Mean magnesium intakes from food for US adults were comparable to Estimated Average Requirement levels for all adult groups, which is consistent with 50% of the population not achieving adequate dietary magnesium intakes. In specific populations of the 2005–2006 NHANES, the magnesium intake was below the Estimated Average Requirement in diets of 48% of North Americans, 89% of teenaged girls, 55–58% of persons aged 51–70 y, and 70–80% of individuals aged  $\geq 71$  y (61, 62).

As a group, adults who use magnesium-containing dietary supplements show a mean magnesium intake above RDA levels (Figure 1); however, their calcium to magnesium

dietary intake ratio is also higher, and it is substantially higher in female supplement users in particular (59, 63–70) (Figure 2).

Dietary intake of magnesium has been low for several decades in the United States (72). In the 1977 USDA nutrient intake survey, the mean magnesium intake from food was 309 mg/d for men (63). In the 2011–2012 NHANES, the mean magnesium intake had increased by 15.5% ( $r = 0.78$ ,  $P = 0.013$ ) to 357 mg/d for men (59), which was still below the RDA of 420 mg/d. In the same 2 surveys, the mean magnesium intake from foods increased from 216 mg/d in 1977 (64) to 271 mg/d in 2011–2012 for women (59), which was an increase of 25% ( $r = 0.93$ ,  $P < 0.001$ ) but was still below the RDA of 320 mg/d. These increases in magnesium intake over the past 33 y were somewhat





**FIGURE 1** Mean magnesium intakes for US women (A) and men (B) from food alone (all adults) and from food plus supplements (supplement users only). Data are from the 2011–2012 NHANES (59) and DRIs (60). In US adults, 23% of women and 22% of men use dietary supplements that contain magnesium (59). EAR, Estimated Average Requirement.

higher but comparable to the increases in food energy between these 2 surveys (i.e., kilocalorie increases of 6% and 17% for men and women, respectively).

### Magnesium physiology

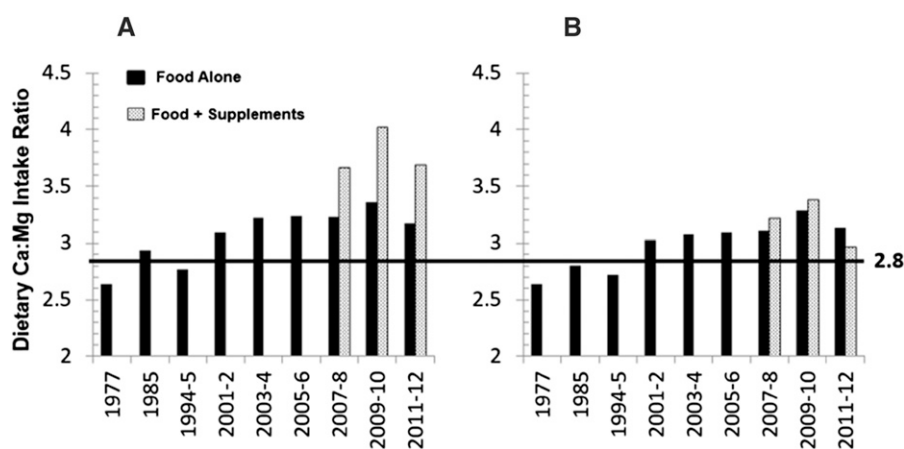
In human adults, whole-body magnesium content is ~24 g (1 mol). Approximately half of this magnesium is present in bone and the other half is found in soft tissue, with <1% present in blood. Serum magnesium represents ~0.3% of whole-body magnesium (73). Although the measurement of serum magnesium is useful in medical diagnoses of clinically severe magnesium deficiency (74), it may not reliably represent whole-body magnesium status. The healthy human body tightly regulates blood magnesium concentrations, maintaining a “normal” range even in times of low dietary magnesium intakes and/or excessive magnesium excretion. Both bone and soft tissue intracellular magnesium concentrations may be depleted (or depleting) while serum/plasma magnesium concentrations remain in the “healthy” range (75). Pig studies in the 1970s (76) showed that magnesium-deficient pigs had reduced intracellular magnesium from soft tissues and erythrocytes as well as reduced bone magnesium content, although serum magnesium remained at the normal concentration. This magnesium physiology appears to be similar in humans (75). Thus, in populations who have chronically low dietary magnesium intakes and high dietary calcium to magnesium ratios, such as in the United States (discussed later in this review),

people who are nonsymptomatic with normal serum magnesium concentrations may have dangerously low tissue magnesium concentrations and decreasing bone magnesium content. This condition has been termed “chronic latent magnesium deficit” (CLMD) (75) and is further considered later in this review.

### Magnesium status assessment

There is currently no simple, reliable biomarker for whole-body magnesium status, and the challenges of assessing magnesium status can impede the interpretation of human magnesium research. The currently available forms of assessment are described below.

**Magnesium load retention test as a biomarker.** The magnesium retention test is cumbersome but is considered the most reliable research indicator of whole-body magnesium status. In this test, an intramuscular or intravenous infusion of magnesium (the magnesium “load”) is given to a subject, followed by urine collection for  $\geq 24$  h. The percentage of the magnesium load excreted in the urine is measured, and the percentage of the magnesium load retained by the body during the length of the urine collection is calculated. Subjects who are magnesium replete are expected to retain small percentages of the magnesium load, whereas subjects with magnesium deficits are expected to show larger retention percentages. Researchers use different retention percentages to define “magnesium deficit” with these load



**FIGURE 2** Increasing calcium to magnesium ratios in US women (A) and men (B) from food alone (all adults) and from food plus supplements (supplement users only). Data are from the USDA Agricultural Research Service Food Surveys for 1977 and 1985 (63, 64), 1994–1995 (65), and 2001–2012 (59, 66–70). In US adults, 23% of women and 22% of men use dietary supplements that contain magnesium (59). A calcium to magnesium ratio >2.8 interacts with a functional polymorphism in colorectal neoplasia risk (71).

**TABLE 2** Varying cutoffs used in magnesium status studies to define hypomagnesemia and magnesium deficit by percentage of magnesium load retention<sup>1</sup>

Authors, year (ref)	Study size and location	Definition of hypomagnesemia by serum magnesium cutoff, mmol/L	Definition of magnesium deficit by magnesium load test (% retention of load)
Arnold et al. 1995 (77)	n = 16; ICU in Wales	<0.6 (reference range: 0.6–1.2)	Retained >30% magnesium load
Saur et al. 1996 (78)	n = 20; ICU in Germany	<0.8 (reference range: 0.8–1.0)	Moderate magnesium deficit: retained >20%–50% magnesium load; considerable magnesium deficit: retained >50% magnesium load
Hébert et al. 1997 (79)	n = 44 renal-sufficient patients; ICU in Ottawa, Canada	<0.7 (reference range: 0.7–0.91)	Retained >30% magnesium load
Ryzen et al. 1985 (80)	n = 94 in large county medical center ICU; Los Angeles, California	<0.74 (reference range: 0.74–0.91)	>40% Retention in 8 h; >15% retention in 24 h; hypomagnesemic patients had 78% retention
Danielson et al. 1979 (81) <sup>2</sup>	n = 106 apparently healthy subjects, aged 15–80 y; Sweden	Women: 0.82 ± 0.06 (n = 47); men: 0.83 ± 0.05 (n = 59); total range: 0.66–0.96	Women: 23% ± 11% retention (n = 12); men: 18% ± 11% retention (n = 22); total range: 0–38%

<sup>1</sup> Magnesium load equals intramuscular or intravenous infusion of magnesium followed by urine collection for ≥24 h when the percentage of magnesium load excreted in urine is calculated. Magnesium-depleted subjects are expected to retain a larger percentage of the load than magnesium-replete subjects. ICU, intensive care unit; ref, reference.

<sup>2</sup> Values for Danielson et al. (81) are presented as serum magnesium means and ranges and magnesium retention means and ranges by magnesium load test.

tests (77–81) (Table 2). In addition to its poorly defined cutoffs and its cumbersome nature, the magnesium load retention test cannot be used in patients with chronic kidney disease or in individuals with critical illnesses (82).

**Serum magnesium and CLMD.** The largest data source for serum magnesium reference ranges is derived from a 1971–1974 US study in 15,820 presumably healthy individuals aged 1–74 y (83), a population who may not have been fully magnesium replete (75). Serum magnesium clinical reference ranges in the United States are not evidence based and may include a subpopulation of unknown size with CLMD. The lower serum magnesium range for healthy individuals has been questioned because some studies suggested that the currently accepted lower range correlates with negative health outcomes. The criterion for low “normal” serum magnesium as a definition for hypomagnesemia

varies widely in studies (Table 2) as well as among clinical laboratories, ranging from as low as 0.6 mmol/L to as high as 0.75 mmol/L (83–85, FH Nielsen, unpublished data, 2015) (Table 3). Increasing the low-normal boundary of serum magnesium to a range of 0.80–0.85 mmol/L to better accommodate the CLMD subpopulation has been suggested (75, 84, 86).

**Magnesium load retention vs. serum magnesium as a biomarker.** Data from a small (n = 16) study in Wales reported both individual serum magnesium and magnesium load retention test results for hospitalized patients (77). The study showed that differentiation between depletion and nondepletion (via the magnesium load retention test) was meaningful only when a serum magnesium value of ≥0.85 mmol/L was used as the cutoff to define hypomagnesemia (77). Serum magnesium may not be a reliable marker

**TABLE 3** Healthy and unhealthy serum magnesium and vitamin D concentrations in commonly used units

	Serum magnesium			Serum vitamin D <sup>1,2</sup>	
	mmol/L	mg/dL	mEq/L	nmol/L	µg/L
1974 NHANES <sup>3</sup>	0.75–0.96	1.82–2.33	1.5–1.92		
High normal <sup>4</sup>	0.91–1.2	2.4–2.9	1.98		
Recommended sufficient <sup>5</sup>	>0.80–0.85	>1.94–2.07	>1.6–1.7		
Low normal <sup>4</sup>	0.60	1.48	1.2		
Low normal <sup>4</sup>	0.70	1.70	1.4		
Low normal <sup>4</sup>	0.75	1.83	1.5		
Adverse				>150	>60
High				>125	>50
Sufficient				50–125	20–50
Inadequate				30–50	12–20
Deficient				<30	<12

<sup>1</sup> Data are from DRIs for calcium and vitamin D (85).

<sup>2</sup> Vitamin D conversion factor: multiply µg/L by 2.5 to convert to nmol/L.

<sup>3</sup> Values are based on the 95% serum magnesium range in 15,820 presumably healthy free-living subjects, aged 1–74 y, in the United States (1971–1974) (83).

<sup>4</sup> Healthy serum magnesium reference ranges vary slightly among clinical laboratories and research studies.

<sup>5</sup> Proposed cutoff range for a more evidence-based definition of hypomagnesemia (84, FH Nielsen, unpublished data, 2015).

of magnesium status in clinical settings or research studies partly because the accepted “normal range” in North America is not evidence based. For example, individuals in the serum magnesium range from 0.6 or 0.7 up to 0.84 mmol/L are labeled “normomagnesemic” and are thus assumed to be non–magnesium depleted when, in fact, a large portion of these persons might more accurately be designated as magnesium depleted. Well-designed studies comparing results of individual magnesium load retention tests with serum magnesium concentrations are needed to fully explore whether increasing the lower cutoff is warranted.

**Value of serum magnesium as a biomarker.** Additional research is needed on the proper use of serum magnesium as a biomarker of magnesium status and the possible impact of CLMD. Studies are needed to address whether there are physiologic changes to bone or soft tissue that are associated with low magnesium intakes but normal serum magnesium concentrations. In addition, proton pump inhibitors are widely prescribed and these medications significantly increase the risk of hypomagnesemia in the general population (87). Recent analysis of human magnesium balance studies suggests that serum magnesium may represent long-term, severely magnesium-deficient status, because it does not respond as rapidly or as flexibly to magnesium intake as does urinary magnesium (FH Nielsen, unpublished data, 2015). At this time, serum magnesium values can be considered a useful, but not an absolutely reliable, indicator of whole-body magnesium status when interpreting human magnesium research.

**Urinary magnesium.** Urinary magnesium increases with high magnesium diets and/or oral magnesium supplementation and remains low during times of low magnesium intake (88, 89). A study by Joosten et al. showed that urinary magnesium excretion is an indicator of intestinal magnesium absorption and is thus a potential marker of CVD risk (90) that is perhaps more reliable than serum magnesium (2, 89).

## Calcium

### Magnesium interactions with calcium

In humans, it has long been known that hypomagnesemia often presents with hypocalcemia (91) and that calcium intake affects magnesium retention and vice versa (see below). Intricate interactions of magnesium and calcium are basic to all living cells and some are quite early on the evolutionary scale (92). For example, it was shown in the amoeba almost a century ago (93) that magnesium prevents calcium entry into the cell when calcium is present in excess. In addition, magnesium prevents calcium exit during calcium-deficient conditions and “in the presence of magnesium, less calcium is required for optimum movement” (93) in these one-celled animals. These basic cellular calcium-magnesium interactions are at work in human cells (94, 95), in which the imbalance of these 2 essential minerals can give rise to cellular phenotypes manifesting the physiologic symptoms of modern chronic diseases (96).

### Change in calcium intake may affect magnesium balance and vice versa

Two comprehensive reviews of pre-1970 human studies on the impact of calcium intake on magnesium balance showed that with magnesium intakes  $<4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ , there was magnesium loss regardless of calcium intake; however, when magnesium intakes were  $\geq 5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ , increases in calcium intake resulted in less magnesium retention (97, 98). Note that the current adult DRIs for magnesium are based on intakes of  $4.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  to maintain balance in healthy adults (60), and human studies found this factor to be  $2.36 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  (95% CI: 1.58,  $3.38 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ) (99). Calcium intakes as high as 2–2.5 g/d caused lower magnesium absorption in 2 small, earlier studies (100, 101). In a study in teenaged girls, magnesium balance was negative with calcium intakes of 1800 mg/d; however, compared with positive magnesium balance results with 800 mg calcium/d, the differences in magnesium absorption, excretion, and balance were not significant in this small crossover trial ( $n = 5$ ) (102). In a randomized clinical trial conducted in New Zealand menopausal women, researchers observed that the consumption of milk high in calcium or supplementation (1200 mg calcium) with or without magnesium significantly increased magnesium urinary excretion during the 8 h of consumption (103). Another trial in Thai menopausal women found that supplementation with 750 mg calcium for 3 mo led to a 15% increase in urinary excretion of magnesium, but the increase was not significant (104). A third trial conducted in women aged 24–34 y in The Netherlands found that 400 mg calcium in the form of salts or in cheese increased urinary excretions of magnesium (105). Although these findings are not entirely consistent and no dietary magnesium intakes were measured, these clinical trials indicate that high calcium supplementation may affect urinary magnesium excretion in women aged  $\geq 24$  y.

With regard to magnesium intakes affecting calcium balance, earlier studies showed that healthy adults with both low magnesium and low calcium intakes had a negative calcium balance, which was attenuated and reversed when magnesium intake improved (97, 98). More recently, a randomized trial of magnesium supplementation, conducted in Ireland, found that increasing magnesium intake from 11 mmol/d (264 mg/d) to  $\sim 22$  mmol/d (528 mg/d) for 28 d did not increase urinary excretion of calcium among women aged 20–28 y (106). Another randomized trial conducted in women aged  $\sim 40$  y in South Africa also found that magnesium supplementation at 250 mg/d (10.3 mmol/d) did not change urinary excretion of calcium, but it reduced fractional absorption of calcium by 23.5%, which was not caused by direct competition between the 2 minerals (107). However, a third trial conducted in men aged 21–42 y in Japan found that supplementation of 250 mg magnesium (as MgO) significantly elevated the urinary excretion of calcium (108). Note that the Japanese population has a low calcium to magnesium ratio (109).

### High calcium to magnesium ratios in the United States

Over the past  $\geq 30$  y in the United States, both dietary calcium and magnesium intakes have increased. However, calcium intakes increased at a rate 2–2.5 times that of dietary magnesium intakes, giving rise to an increasing calcium to magnesium ratio in this population (Figure 2). This trend appears to have either reversed or leveled off during 2011–2012, but further surveys are needed to determine which trend, if either, is occurring. Compared with the increases in mean magnesium intakes in US adults (increases of 15.5% and 25% for men and women, respectively; see above) from 1977 to 2011–2012, mean calcium intakes from these same surveys (59, 63–70) showed increases of 37% in men (from 815 to 1117 mg calcium/d;  $r = 0.92$ ,  $P = 0.0005$ ) and 51% in women (from 570 to 862 mg calcium/d;  $r = 0.95$ ,  $P = 0.0001$ ). As a result, the mean calcium to magnesium ratio in US adults increased significantly between 1977 and 2012 (for men:  $r = 0.92$ ,  $P = 0.0005$ ; for women:  $r = 0.89$ ,  $P = 0.001$ ); in 2001, the mean calcium to magnesium ratio increased from  $<3.0$  to  $>3.0$  for both men and women (Figure 2). Increases in mean calcium and magnesium intakes were 3–6 and 1.5–3 times the increases in kilocalories, respectively (17% for women and 6% for men). This high calcium to magnesium ratio appears to be exacerbated by supplement usage, especially in women (110).

### Impact of calcium to magnesium ratios on disease outcomes

Traditional advice is to maintain dietary calcium to magnesium ratios close to 2.0 for optimal health outcomes in humans (111) came from knowledgeable speculation that was not supported by any experimental evidence. In 2007, a colorectal neoplasia study by Dai et al. (71) provided evidence for an optimal dietary calcium to magnesium ratio (i.e.,  $<2.8$ ). In this case-control study ( $n = 2204$ ), the risk of colorectal adenoma was reduced only in subjects with a calcium to magnesium ratio  $<2.8$ , although this risk decreased with increasing total magnesium intakes regardless of confounders. Among those with a calcium to magnesium ratio  $>2.8$ , total magnesium intake was not related to risk, although increasing total calcium intake showed a trend toward greater risk. Thus, total calcium intakes may be related to a reduced risk of colorectal adenoma only when calcium to magnesium ratios are  $<2.8$ . Dai et al. also found a nutrient-gene interaction [i.e., transient receptor potential melastatin 7 (*TRPM7*) with dietary Ca:Mg] in relation to the risk of both colorectal adenoma and hyperplastic polyps. *TRPM7* is a newly identified gene that is essential to magnesium homeostasis, and the Thr14821le rs8042919 polymorphism in the *TRPM7* gene is functional. Individuals with the 14821le allele and calcium to magnesium ratios  $>2.8$  had a 60% greater risk of colorectal adenoma and an 85% increased risk of hyperplastic polyps than those without the 14821le allele in the *TRPM7* gene (71).

A follow-up randomized clinical trial in 930 subjects (112) found that long-term calcium treatment (1200 mg/d over a 4-y period) significantly reduced colorectal adenoma recurrence risk but only when the baseline calcium to magnesium ratio was  $<2.6$  (RR: 0.68; 95% CI: 0.52, 0.90). By contrast, calcium supplementation had no effect among subjects when the calcium to magnesium ratio was  $>2.6$  (RR: 0.98; 95% CI: 0.75, 1.2). This effect modification by the calcium to magnesium ratio cannot solely be attributed to the baseline dietary intake of calcium or magnesium (112). These results show that the interpretation of studies measuring either calcium or magnesium intake alone is difficult, especially because food sources of calcium and magnesium are positively correlated (113).

### Opposite influence of low calcium to magnesium ratios on health outcomes

Just as a calcium to magnesium ratio  $>2.6$ – $2.8$  can result in a detrimental effect, baseline calcium to magnesium ratios  $<2.0$  may also have a detrimental effect. The Shanghai Women's Health Study and the Shanghai Men's Health Study are 2 population-based cohorts with  $>130,000$  participants. These studies were conducted in a Chinese population in whom magnesium intakes are comparable to the US population; however, the median calcium to magnesium ratio ( $\sim 1.7$ ) is much lower than the calcium to magnesium ratio in the US population ( $\geq 3.0$ ) (114). In this population with very low calcium to magnesium ratios, magnesium intakes at or above RDA levels were associated with an increased risk of total mortality in both women and men. This is in contrast with US studies undertaken with a high background calcium to magnesium ratio ( $\geq 3.0$ ), which showed decreased mortality when magnesium intakes were increased by 200–375 mg/d (7, 13, 115, 116).

Furthermore, in the Chinese studies, among those with calcium to magnesium ratios  $>1.7$ , a magnesium intake  $\geq 320$  mg/d was significantly associated with reduced risks of total mortality and mortality due to ischemic heart disease (IHD) among men and mortality due to all cancers among women. By contrast, when calcium to magnesium ratios were  $\leq 1.7$ , magnesium intake  $\geq 320$  mg/d was significantly related to increased risks of all-cause mortality and mortality due to CVD and colorectal cancer among women.

In addition, one study measuring both serum calcium and magnesium found that elevated serum magnesium was significantly associated with a lower risk of high-grade prostate cancer (OR: 0.26; 95% CI: 0.09, 0.85), whereas an elevated serum calcium to magnesium ratio was associated with an increased risk of high-grade prostate cancer (OR: 2.81; 95% CI: 1.24, 6.36) adjusted for serum calcium and magnesium (50). Another study with an examination of serum concentrations of calcium, magnesium, and phosphorus in a large population of whites and African Americans (27%) indicated that when serum magnesium is low and calcium and phosphorus are higher, this leads to a greater risk of heart failure (117). With the use of NHANES data, a recent study found that women who met the RDA for



both magnesium and calcium had the greatest reduced odds of MetS (OR: 0.59; 95% CI: 0.45, 0.76). In men, meeting the RDA showed no association with MetS, but those with intakes in the highest quartile for magnesium ( $\geq 386$  mg/d) and calcium ( $\geq 1224$  mg/d) had lower odds of MetS (OR: 0.74; 95% CI: 0.59, 0.93) (118).

In skeletal studies, magnesium depletion was associated with decreased osteoblastic and increased osteoclastic activity (40), lower bone mineral density (BMD) (32, 34, 36), and fragility. Most studies suggest that magnesium intake favorably alters BMD. In a study by Orchard et al. (33) that used data from the Women's Health Initiative, a lower magnesium intake was associated with lower BMD of the hip and whole body, as expected; however, this did not translate into an increased risk of hip or total fractures. In the same study, excess magnesium appeared to be detrimental to bone and fracture risk of the forearm and wrist. The authors speculated that greater physical activity, made more likely by increased magnesium intakes, was responsible for this unexpected result. It would have been interesting to see whether calcium intakes and calcium to magnesium ratios might have further explained this detrimental outcome of higher magnesium intakes (33).

Together, these findings suggest that any magnesium or calcium effect is dependent on the intake amount of calcium or magnesium, respectively, and thus on the calcium to magnesium ratio. Furthermore, dietary intake studies of either magnesium or calcium alone may be unwittingly confounded by the unmeasured calcium or magnesium. These findings are relevant to the US population (and other populations experiencing an increased Ca:Mg) because the calcium to magnesium ranges that show these modifying effects (i.e.,  $<1.7$  in the Chinese study and  $>2.6$ – $2.8$  in the US studies) are well below the current mean calcium to magnesium ratio in US adults, which was 3.1–3.2 in 2007–2008 (119) and increased to 3.3–3.4 in 2009–2010 (Figure 2) from food intakes alone (i.e., not including supplements).

It appears that too much or too little of either calcium or magnesium might not be beneficial and there may be an optimal range of human calcium and magnesium intake. Studies in this area might expand our knowledge of when supplementation with magnesium or calcium is helpful or detrimental. Long-term exposure to a diet with a high calcium to magnesium ratio, which is common in the United States, may lead to public health concerns and requires further study.

## Vitamin D

### Magnesium interactions with vitamin D

There has been a recent surge of positive studies for several human health issues with vitamin D in the peer-reviewed literature, giving rise to medical prescriptions for and over-the-counter sales of high doses of vitamin D to increase serum vitamin D concentrations. With early studies showing an effect of magnesium on vitamin D status in patients with clinically diagnosed magnesium deficiency (23, 120–125), it

is important to review the possible effects of both nutrients on one another in a general population with largely suboptimal magnesium intake (see above).

### Vitamin D Status

Vitamin D deficiency causes rickets in children and osteomalacia in adults (126). Many epidemiologic studies suggest that low vitamin D status may also be associated with all-cause mortality (127–129) and with the risk of nonskeletal chronic diseases such as T2D (130–132), CVD (133, 134), and colorectal cancer (135–137). However, findings have not been entirely consistent (138–141). Large-scale clinical trials of vitamin D supplementation are ongoing (138, 139, 142). Despite food fortification and dietary supplementation, low vitamin D status ( $<20$   $\mu\text{g/L}$  or  $<50$   $\text{nmol/L}$ ; Table 3) is still relatively common in the United States (143). In addition, there is large interindividual variation in serum 25-hydroxyvitamin D [25(OH)D] concentrations that is unexplained by dietary intake of vitamin D and sun exposure alone (144, 145).

### Magnesium is a cofactor in several steps of vitamin D biosynthesis and activation

Magnesium, the second most abundant intracellular cation, plays a critical role in the synthesis and metabolism of parathyroid hormone (PTH) and vitamin D (123, 146, 147). Previous studies showed that the activities of 3 major enzymes that determine 25(OH)D concentrations, 25-hydroxylase,  $1\alpha$ -hydroxylase, and 24-hydroxylase (123, 147, 148), as well as vitamin D binding protein (VDBP) (123), are magnesium dependent. Magnesium deficiency leads to reduced 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}$ ] and impaired PTH response (123) and has been implicated in magnesium-dependent, vitamin D-resistant rickets (146). In 2 case studies of vitamin D-resistant rickets, magnesium supplementation substantially reversed the resistance to vitamin D treatment (146), whereas intramuscular infusion of vitamin D as high as 600,000 IU alone did not lead to any improvement in biochemical features of advanced vitamin D deficiency (i.e., serum calcium, magnesium, phosphorus, and alkaline phosphatase; serum vitamin D was not measured) (146). On the other hand, 2 small clinical studies with no placebo arm conducted in magnesium-deficient patients (123, 149) found that magnesium infusion alone led to a nonsignificant increase in both 25(OH)D and  $1,25(\text{OH})_2\text{D}$  (123), whereas magnesium infusion plus oral vitamin D as 25(OH)D substantially increased both serum 25(OH)D and  $1,25(\text{OH})_2\text{D}$  (149). Thus, these findings showed no effect for a high dose of vitamin D alone or magnesium infusion alone; however, there was a substantial increase in serum 25(OH)D due to vitamin D supplementation with magnesium infusion. Taken together, these findings suggest that a possible interaction between magnesium and vitamin D influences vitamin D status (150), but these findings should be tested in a large clinical trial.

### Effects of interaction between nutritional magnesium status and serum vitamin D on disease outcomes

On the basis of this biological plausibility, one recent NHANES study found that a high intake of total, dietary, or supplemental magnesium was independently and significantly associated with reduced risks of both vitamin D deficiency and insufficiency in the general population (150). In addition, an inverse association between total magnesium intake and vitamin D insufficiency primarily appeared among populations at high risk of vitamin D insufficiency, such as overweight/obese individuals and African Americans. Furthermore, this study also found inverse associations of serum 25(OH)D with mortality (particularly CVD and colorectal cancer) that were modified by high magnesium intake (i.e., the inverse associations were primarily present when the magnesium intake was above the median).

The critical role of magnesium in the synthesis of VDBP, PTH, 25(OH)D, and 1,25(OH)<sub>2</sub>D may partially explain why these inverse associations between serum 25(OH)D and the risk of all-cause mortality and mortality due to colorectal cancer and CVD primarily existed among those with magnesium intakes above the median. High magnesium intakes may increase the availability of 1,25(OH)<sub>2</sub>D by activating the synthesis of 25(OH)D and 1,25(OH)<sub>2</sub>D and increasing the transfer to target tissues by elevating VDBP. This explanation is supported by 2 case studies reported by Reddy and Sivakumar (146), in which magnesium supplementation substantially reversed the resistance to vitamin D treatment in magnesium-deficient patients.

A previous clinical study found that parenteral magnesium treatment without vitamin D replacement in 23 magnesium-deficient patients led to a normalizing of VDBP. The study also reported a 12% increase in serum 25(OH)D and a 30% increase in serum 1,25(OH)<sub>2</sub>D; however, neither of these changes was significant (123). In a subsequent study in 5 magnesium-deficient patients, intramuscular treatment with magnesium alone did not significantly increase serum 25(OH)D, but magnesium infusion together with a pharmacologic dose of 25(OH)D substantially increased both serum 25(OH)D and 1,25(OH)<sub>2</sub>D among patients with magnesium deficiency (149). One interpretation is that magnesium treatment does not affect 25(OH)D status (123, 149). However, it is also possible that several factors may have contributed to the nonsignificant increase in 25(OH)D status. First, the patients with magnesium deficiency who participated in these previous studies had low concentrations of 25(OH)D and 1,25(OH)<sub>2</sub>D as well as pre-vitamin D<sub>3</sub> and vitamin D<sub>3</sub> (cholecalciferol) as a result of limited sunlight exposure, underlying disease, and/or lack of oral supplementation. Therefore, concentrations of 25(OH)D and 1,25(OH)<sub>2</sub>D did not substantially increase during short-term magnesium repletion because pre-vitamin D<sub>3</sub> was not available in sufficient amounts. Second, a modest increase in the conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D resulted in a reduction in 25(OH)D concentrations (147). Finally, the sample size in

these 2 studies may have been too small to show a significant moderate effect of magnesium treatment on vitamin D status.

### Similar health effects of vitamin D and magnesium studies

Vitamin D and magnesium studies have shown similar associations in several aspects of human health (151) (Table 1). In these areas of human disease, vitamin D and magnesium may potentially confound each other or a possible interaction between the 2 may exist. However, almost all studies in these areas measured either vitamin D or magnesium status, not both. This may hamper interpretation of the results. For example, results of studies examining associations between magnesium intake and risk of stroke (6, 152) and IHD (116, 152) have been inconsistent. A meta-analysis of prospective studies found that magnesium intake was related to a significantly reduced risk of stroke; however, this inverse association was weak (an 8% reduction in risk per 100-mg magnesium/d increment) and only 1 of the 7 cohorts included in the meta-analysis found a significant inverse association (6). Likewise, a prospective cohort study showed that magnesium intake was nonsignificantly inversely associated with IHD, with a pooled RR of 0.86 (95% CI: 0.67, 1.10) for the highest quintile (mean magnesium intake: 433 mg/d) vs. the lowest quintile (mean magnesium intake: 255 mg/d) of intake category (152). However, it must be noted that 255 mg magnesium/d was found to be adequate for healthy human adults in a series of metabolic unit magnesium balance studies (99). Similar to these findings in studies on stroke and IHD, several studies evaluated the associations between magnesium intake and the risk of colorectal adenoma and cancer and the results were also not entirely consistent (48, 71, 153, 154). All of these studies examined associations of disease with magnesium intake only, without considering any interaction with vitamin D. The significant interactions between serum vitamin D and magnesium intakes in relation to mortality due to CVD and colorectal cancer might help to explain such inconsistencies.

Although findings on the potential interaction between vitamin D and magnesium have been promising, only one recent study, to our knowledge, examined the interaction between vitamin D and magnesium in the general population (150). Deng et al. (150) found that magnesium intake may contribute to vitamin D status and that associations between serum vitamin D and mortality risk may be modified by magnesium intake. Because there is currently only one available study, it is difficult to discern whether these 2 micronutrients act independently or synergistically. Future studies are warranted to replicate the findings of Deng et al. and to explore the biochemical basis and molecular mechanisms that would explain these findings.

### Areas in need of study on the interaction between magnesium, calcium, and vitamin D

Normal vitamin D metabolism requires Mg<sup>2+</sup> for its synthesis and metabolism of parathyroid hormone and vitamin D

(see above). The following questions require further exploration: Does low magnesium status affect this activation? Does the calcium to magnesium ratio affect this activation? Does low magnesium status result in low serum 25(OH)D concentrations? Is there an impact of the calcium to magnesium ratio on serum 25(OH)D concentrations? When discerning clinical, biochemical, or physiologic effects of low serum vitamin D, are these effects all or partly due to a low magnesium status or a high calcium to magnesium ratio? Do clinical aspects of magnesium deficit or suboptimal status really derive at least partially from low serum vitamin D associated with low magnesium status or a high calcium to magnesium ratio? Does vitamin D supplementation affect magnesium status in any manner?

Seelig (97, 98) reviewed earlier studies on animals, summarizing that vitamin D supplements improved both calcium and magnesium absorption but also increased magnesium excretion and therefore decreased magnesium retention. In one well-controlled human study (155), added vitamin D caused a decrease in magnesium retention, as predicted by animal studies. This area requires further study.

Dietary phosphorus interacts with each of the 3 above-described nutrients (magnesium, calcium, and vitamin D) and dietary intakes of phosphorus in US adults are well above the RDA of 700 mg/d. Phosphorus intakes in the United States have remained relatively stable, as have magnesium intakes, compared with the substantial increase in calcium intakes since 1977. Not much is known about the interaction of magnesium with phosphorus; however, because phosphorus is closely linked to calcium, it is possible that phosphorus nutrition affects a population with low magnesium dietary intakes. Indeed, Lutsey et al. (117) found that lower serum magnesium coupled with high serum calcium and phosphorus was a risk factor for heart failure. Interactions of phosphorus with magnesium, calcium, and vitamin D are areas for future study.

## Conclusions

The essential micronutrients magnesium, calcium, and vitamin D are each associated with chronic diseases of global concern, including CVD, T2D, MetS, and skeletal disorders. Dietary intakes of magnesium in the US population are low, and dietary calcium intakes in US adults increased 2–2.5 times more than dietary magnesium intakes between 1977 and 2010. Oral vitamin D has recently been recommended and is widely available. Despite these changes in intakes, research on the interactions between these 3 essential nutrients has been sparse.

Measuring magnesium status presents challenges, but magnesium intake is low in populations who consume a modern processed-food diet, including individuals in the United States. High calcium intakes can exacerbate the onset of low magnesium status and vice versa. Studies showed that a calcium to magnesium intake ratio <2.8 is critical for optimal health, supporting a long-held but non-evidence-based recommendation that the calcium to magnesium ratio should be close to 2. Increasing calcium intakes in the United States

since 1977 have resulted in a calcium to magnesium ratio >3.0 since 2000, coinciding with increasing rates of T2D and colorectal cancer. US studies assessing oral magnesium therapy or dietary magnesium intakes showed beneficial effects of dietary magnesium in CVD, T2D, and cancers, although similar studies in populations with lower calcium to magnesium ratios ( $\geq 1.7$ ) reported the opposite, showing the impact that background dietary calcium and/or magnesium can have on studies of either calcium or magnesium alone.

Low vitamin D status is associated with chronic diseases of global concern, as is low magnesium status. Magnesium is a cofactor for vitamin D biosynthesis, transport, and activation. Interactions between magnesium intake and serum vitamin D contributing to the risk of CVD and colorectal cancer were recently indicated. However, epidemiologic data on possible interactions of these 2 micronutrients in human health and disease are very limited. Thus, additional studies are warranted. Increasing calcium to magnesium ratios coupled with oral calcium and vitamin D supplement recommendations in the face of suboptimal magnesium intakes may be affecting health via unstudied impacts of interactions between magnesium, calcium, and vitamin D.

## Acknowledgments

All authors read and approved the final manuscript.

## References

1. Seelig M, Rosanoff A. Are we really low in magnesium? In: Seelig M, Rosanoff A, editors. *The magnesium factor*. New York: Avery, Penguin; 2003. p. 211–8.
2. Joosten MM, Gansevoort RT, Mukamal KJ, van der Harst P, Geleijnse JM, Feskens EJ, Navis G, Bakker SJ; Prevend Study Group. Urinary and plasma magnesium and risk of ischemic heart disease. *Am J Clin Nutr* 2013;97:1299–306.
3. Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, Magnani JW, Ellinor PT, Benjamin EJ, Wang TJ. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. *Circulation* 2013;127:33–8.
4. Misialek JR, Lopez FL, Lutsey PL, Huxley RR, Peacock JM, Chen LY, Soliman EZ, Agarwal SK, Alonso A. Serum and dietary magnesium and incidence of atrial fibrillation in whites and in African Americans—Atherosclerosis Risk in Communities (ARIC) study. *Circ J* 2013; 77:323–9.
5. Del Gobbo LC, Song Y, Poirier P, Dewailly E, Elin RJ, Egeland GM. Low serum magnesium concentrations are associated with a high prevalence of premature ventricular complexes in obese adults with type 2 diabetes. *Cardiovasc Diabetol* 2012;11:23.
6. Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *Am J Clin Nutr* 2012;95: 362–6.
7. Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2013;98:160–73.
8. Qu X, Jin F, Hao Y, Li H, Tang T, Wang H, Yan W, Dai K. Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. *PLoS One* 2013;8:e57720.
9. Nie ZL, Wang ZM, Zhou B, Tang ZP, Wang SK. Magnesium intake and incidence of stroke: meta-analysis of cohort studies. *Nutr Metab Cardiovasc Dis* 2013;23:169–76.



10. Alghamdi AA, Al-Radi OO, Latter DA. Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. *J Card Surg* 2005;20:293–9.
11. Shiga T, Wajima Z, Inoue T, Ogawa R. Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. *Am J Med* 2004;117:325–33.
12. Reffelmann T, Ittermann T, Dorr M, Volzke H, Reinthaler M, Petersmann A, Felix SB. Low serum magnesium concentrations predict cardiovascular and all-cause mortality. *Atherosclerosis* 2011;219:280–4.
13. Chiuve SE, Sun Q, Curhan GC, Taylor EN, Spiegelman D, Willett WC, Manson JE, Rexrode KM, Albert CM. Dietary and plasma magnesium and risk of coronary heart disease among women. *J Am Heart Assoc* 2013;2:e000114.
14. Booth JV, Phillips-Bute B, McCants CB, Podgoreanu MV, Smith PK, Mathew JP, Newman MF. Low serum magnesium level predicts major adverse cardiac events after coronary artery bypass graft surgery. *Am Heart J* 2003;145:1108–13.
15. Ishimura E, Okuno S, Yamakawa T, Inaba M, Nishizawa Y. Serum magnesium concentration is a significant predictor of mortality in maintenance hemodialysis patients. *Magnes Res* 2007;20:237–44.
16. Singhi SC, Singh J, Prasad R. Hypo- and hypermagnesemia in an Indian pediatric intensive care unit. *J Trop Pediatr* 2003;49:99–103.
17. Dong JY, Xun P, He K, Qin LQ. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. *Diabetes Care* 2011;34:2116–22.
18. Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. *J Intern Med* 2007;262:208–14.
19. Sales CH, Pedrosa LF, Lima JG, Lemos TM, Colli C. Influence of magnesium status and magnesium intake on the blood glucose control in patients with type 2 diabetes. *Clin Nutr* 2011;30:359–64.
20. Agrawal P, Arora S, Singh B, Manamalli A, Dolia PB. Association of macrovascular complications of type 2 diabetes mellitus with serum magnesium levels. *Diabetes Metab Syndr* 2011;5:41–4.
21. Sharma A, Dabla S, Agrawal RP, Barjatya H, Kochar DK, Kothari RP. Serum magnesium: an early predictor of course and complications of diabetes mellitus. *J Indian Med Assoc* 2007;105:16, 8, 20.
22. Chambers EC, Heshka S, Gallagher D, Wang J, Pi-Sunyer FX, Pierson RN Jr. Serum magnesium and type-2 diabetes in African Americans and Hispanics: a New York cohort. *J Am Coll Nutr* 2006;25:509–13.
23. Saggese G, Federico G, Bertelloni S, Baroncelli GI, Calisti L. Hypomagnesemia and the parathyroid hormone-vitamin D endocrine system in children with insulin-dependent diabetes mellitus: effects of magnesium administration. *J Pediatr* 1991;118:220–5.
24. Solati M, Ouspid E, Hosseini S, Soltani N, Keshavarz M, Dehghani M. Oral magnesium supplementation in type II diabetic patients. *Med J Islam Repub Iran* 2014;28:67.
25. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med* 2006;23:1050–6.
26. Yang CY, Chiu HF, Cheng MF, Tsai SS, Hung CF, Tseng YT. Magnesium in drinking water and the risk of death from diabetes mellitus. *Magnes Res* 1999;12:131–7.
27. He K, Liu K, Daviglius ML, Morris SJ, Loria CM, Van Horn L, Jacobs DR Jr., Savage PJ. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006;113:1675–82.
28. Huang JH, Lu YF, Cheng FC, Lee JN, Tsai LC. Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study. *Nutr J* 2012;11:41.
29. Guerrero-Romero F, Rodríguez-Moran M. Low serum magnesium levels and metabolic syndrome. *Acta Diabetol* 2002;39:209–13.
30. Rodríguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves the metabolic profile of metabolically obese, normal-weight individuals: a randomized double-blind placebo-controlled trial. *Arch Med Res* 2014;45:388–93.
31. Dibaba DT, Xun P, Fly AD, Yokota K, He K. Dietary magnesium intake and risk of metabolic syndrome: a meta-analysis. *Diabet Med* 2014a;31:1301–9.
32. Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr* 1999;69:727–36.
33. Orchard TS, Larson JC, Alghothani N, Bout-Tabaku S, Cauley JA, Chen Z, Lacroix AZ, Wactawski-Wende J, Jackson RD. Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Observational Study. *Am J Clin Nutr* 2014;99:926–33.
34. Ryder KM, Shorr RI, Bush AJ, Kritchevsky SB, Harris T, Stone K, Cauley J, Tyllavsky FA. Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. *J Am Geriatr Soc* 2005;53:1875–80.
35. New SA, Robins SP, Campbell MK, Martin JC, Garton MJ, Bolton-Smith C, Grubb DA, Lee SJ, Reid DM. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? *Am J Clin Nutr* 2000;71:142–51.
36. Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. *Magnes Res* 1993;6:155–63.
37. Hopping BN, Erber E, Grandinetti A, Verheus M, Kolonel LN, Maskarinec G. Dietary fiber, magnesium, and glycemic load alter risk of type 2 diabetes in a multiethnic cohort in Hawaii. *J Nutr* 2010;140:68–74.
38. Hruby A, McKeown N, Song Y, Djoussé L. Dietary magnesium and genetic interactions in diabetes and related risk factors: a brief overview of current knowledge. *Nutrients* 2013;5:4990–5011.
39. Guasch-Ferré M, Bullo M, Estruch R, Corella D, Martínez-González MA, Ros E, Covas M, Aros F, Gomez-Gracia E, Fiol M, et al. Dietary magnesium intake is inversely associated with mortality in adults at high cardiovascular disease risk. *J Nutr* 2014;144:55–60.
40. Rude RK, Singer FR, Gruber HE. Skeletal and hormonal effects of magnesium deficiency. *J Am Coll Nutr* 2009;28:131–41.
41. Sojka JE, Weaver CM. Magnesium supplementation and osteoporosis. *Nutr Rev* 1995;53:71–4.
42. New SA, Bolton-Smith C, Grubb DA, Reid DM. Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. *Am J Clin Nutr* 1997;65:1831–9.
43. Aziz HS, Blamoun AI, Shubair MK, Ismail MM, DeBari VA, Khan MA. Serum magnesium levels and acute exacerbation of chronic obstructive pulmonary disease: a retrospective study. *Ann Clin Lab Sci* 2005;35:423–7.
44. Bhatt SP, Khandelwal P, Nanda S, Stoltzfus JC, Fioravanti GT. Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease. *Respir Med* 2008;102:999–1003.
45. Fiaccadori E, Del Canale S, Coffrini E, Melej R, Vitali P, Guariglia A, Borghetti A. Muscle and serum magnesium in pulmonary intensive care unit patients. *Crit Care Med* 1988;16:751–60.
46. Kurys E, Kurys P, Kuzniar A, Kieszko R. Analysis of antioxidant enzyme activity and magnesium level in chronic obstructive pulmonary disease (COPD). *Ann Univ Mariae Curie Sklodowska Med* 2001;56:261–6.
47. Ruljancic N, Popovic-Grlje S, Rumenjak V, Sokolic B, Malic A, Mihanovic M, Cepelak I. COPD: magnesium in the plasma and polymorphonuclear cells of patients during a stable phase. *COPD* 2007;4:41–7.
48. Chen GC, Pang Z, Liu QF. Magnesium intake and risk of colorectal cancer: a meta-analysis of prospective studies. *Eur J Clin Nutr* 2012;66:1182–6.
49. Ko HJ, Youn CH, Kim HM, Cho YJ, Lee GH, Lee WK. Dietary magnesium intake and risk of cancer: a meta-analysis of epidemiologic studies. *Nutr Cancer* 2014;66:915–23.
50. Dai Q, Motley SS, Smith JA Jr., Concepcion R, Barocas D, Byerly S, Fowke JH. Blood magnesium, and the interaction with calcium, on the risk of high-grade prostate cancer. *PLoS One* 2011;6:e18237.
51. Everett CJ, King DE, Wells BJ, Frithsen IL, Mainous AG III. Serum magnesium and cancer mortality. In: Bernhardt NE, Kasko AM, editors. *Nutrition for the middle aged and elderly*. Hauppauge (NY): Nova Science Publishers; 2008. p. 271–84.



52. Barragan-Rodríguez L, Rodríguez-Moran M, Guerrero-Romero F. Depressive symptoms and hypomagnesemia in older diabetic subjects. *Arch Med Res* 2007;38:752–6.
53. Derom ML, Sayon-Orea C, Martínez-Ortega JM, Martínez-Gonzalez MA. Magnesium and depression: a systematic review. *Nutr Neurosci* 2013;16:191–206.
54. Tarleton EK, Littenberg B. Magnesium intake and depression in adults. *J Am Board Fam Med* 2015;28:249–56.
55. Yary T, Aazami S, Soleimannejad K. Dietary intake of magnesium may modulate depression. *Biol Trace Elem Res* 2013;151:324–9.
56. Ozawa M, Ninomiya T, Ohara T, Hirakawa Y, Doi Y, Hata J, Uchida K, Shirota T, Kitazono T, Kiyohara Y. Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in the Japanese: the Hisayama Study. *J Am Geriatr Soc* 2012;60:1515–20.
57. Slutsky I, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Zhuo M, et al. Enhancement of learning and memory by elevating brain magnesium. *Neuron* 2010;65:165–77.
58. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128. Erratum in: *Lancet* 2013;381(9867):628.
59. USDA Agricultural Research Service. What we eat in America, NHANES 2011–2012. Table 37: Total nutrient intakes: percent reporting and mean amounts of selected vitamins and minerals from food and beverages and dietary supplements, by gender and age, in the United States, 2011–2012. Magnesium [cited 2015 Jan 1]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/1112/Table\\_37\\_SUP\\_GEN\\_11.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/1112/Table_37_SUP_GEN_11.pdf).
60. Institute of Medicine. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington (DC): National Academies Press; 1997.
61. Moshfegh A, Goldman JD, Ahuja J, Rhodes D, LaComb R. What we eat in America, NHANES 2005–2006: usual nutrient intakes from food and water compared to 1997 Dietary Reference Intakes for vitamin D, calcium, phosphorus, and magnesium. 2009 [cited 2015 May 11]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/0506/usual\\_nutrient\\_intake\\_vitD\\_ca\\_phos\\_mg\\_2005-06.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/0506/usual_nutrient_intake_vitD_ca_phos_mg_2005-06.pdf).
62. Rosanoff A, Weaver CM, Rude RK. Suboptimal magnesium status in the United States: are the health consequences underestimated? *Nutr Rev* 2012;70:153–64.
63. USDA Human Nutrition Information Service. CSFII Nationwide Food Consumption Survey Continuing Survey of Food Intakes by Individuals; men 19–50 years, 1 day; report no. 85–3. 1985 [cited 2012 Jul 10]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/8586/csfii85\\_1day\\_men\\_doc.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/8586/csfii85_1day_men_doc.pdf).
64. USDA Human Nutrition Information Service. CSFII Nationwide Food Consumption Survey Continuing Survey of Food Intakes by Individuals; women 19–50 years and their children 1–5 years, 1 day; report no. 85–1. 1985 [cited 2012 Jul 10]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/8586/csfii85\\_1day\\_women\\_doc.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/8586/csfii85_1day_women_doc.pdf).
65. Wilson JW, Enns CW, Goldman JD, Tippett KS, Mickle SJ, Cleveland LE, Chahil PS. Data tables: combined results from USDA's 1994 and 1995 Diet and Health Knowledge Survey [online]. 1997 [cited 2012 Jul 10]. Available from: <http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm>; <http://www.ars.usda.gov/Services/docs.htm?docid=14531>.
66. USDA Agricultural Research Service. Nutrient intakes from food compared to Dietary Reference Intakes. Table 1. Mean amounts by gender and age: individuals 2 years and over (excluding breast-fed children), MEC sampling weights NHANES, 2001–2002 [cited 2012 Feb 29]. Available from: <http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0102/usualintaketables2001-02.pdf>.
67. USDA Agricultural Research Service. Table 1. Nutrient intakes from food: mean amounts consumed per individual, one day, NHANES 2003–2004. 2007 [cited 2012 Feb 29]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0304/Table\\_1\\_NIF.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0304/Table_1_NIF.pdf).
68. USDA Agricultural Research Service. Table 1. Nutrient intakes from food: mean amounts consumed per individual, one day, NHANES 2005–2006. 2008 [cited 2012 Feb 29]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0506/Table\\_1\\_NIF\\_05.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0506/Table_1_NIF_05.pdf).
69. USDA Agricultural Research Service. Table 1. Nutrient intakes from food: mean amounts consumed per individual, one day, NHANES 2007–2008. 2010 [cited 2012 Feb 29]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0708/Table\\_1\\_NIN\\_GEN\\_07.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0708/Table_1_NIN_GEN_07.pdf).
70. USDA Agricultural Research Service. What we eat in America, NHANES 2009–2010, individuals 2 years and over (excluding pregnant and/or lactating females and breast-fed children), day 1 food and supplement intake data, weighted. 2012 [cited 2014 Oct 15]. Available from: [http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0910/Table\\_39\\_SUP\\_INC\\_09.pdf](http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/0910/Table_39_SUP_INC_09.pdf).
71. Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE, Li M, Shyr Y, Zheng W. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 2007;86:743–51.
72. Marier JR. Magnesium content of the food supply in the modern-day world. *Magnesium* 1986;5:1–8.
73. Elin RJ. Laboratory tests for the assessment of magnesium status in humans. *Magn Trace Elem* 1991;10:172–81.
74. Wong ET, Rude RK, Singer FR, Shaw ST Jr. A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. *Am J Clin Pathol* 1983;79:348–52.
75. Elin RJ. Assessment of magnesium status for diagnosis and therapy. *Magn Res* 2010;23:S194–8.
76. Nuoranne P. On the reliability of the magnesium serum value as an indicator of body magnesium status. *Nord Vet Med* 1978;30:71–3.
77. Arnold A, Tovey J, Mangat P, Penny W, Jacobs S. Magnesium deficiency in critically ill patients. *Anaesthesia* 1995;50:203–5.
78. Saur PM, Zielmann S, Roth AT, Frank L, Warneke G, Radke A, Ensink FB, Kettler D. [Diagnosis of magnesium deficiency in intensive care patients.] *Anesthesiol Intensivmed Notfallmed Schmerzther* 1996;31:37–41 (in German).
79. Hébert P, Mehta N, Wang J, Hindmarsh T, Jones G, Cardinal P. Functional magnesium deficiency in critically ill patients identified using a magnesium-loading test. *Crit Care Med* 1997;25:749–55.
80. Ryzen E, Elbaum N, Singer FR, Rude RK. Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. *Magnesium* 1985;4:137–47.
81. Danielson BG, Johansson G, Ljunghall S. Magnesium metabolism in healthy subjects. *Scand J Urol Nephrol Suppl* 1979;49–73.
82. Seelig MS. Magnesium deficiency in the pathogenesis of disease, early roots of cardiovascular, skeletal, and renal abnormalities. New York and London: Plenum Medical Book Co.; 1980.
83. Lowenstein FW, Stanton MF. Serum magnesium levels in the United States, 1971–1974. *J Am Coll Nutr* 1986;5:399–414.
84. Elin RJ. Re-evaluation of the concept of chronic, latent, magnesium deficiency. *Magn Res* 2011;24:225–7.
85. Ross AC, Taylor CL, Yaktine AL, Del Valle H. Dietary Reference Intakes for calcium and vitamin D. Washington (DC): National Academies Press; 2011.
86. Elin R. Laboratory evaluation of chronic latent magnesium deficiency. In: Rayssiguier Y, Mazur A, Durlach J, editors. *Advances in magnesium research: nutrition and health*. Eastleigh (United Kingdom): John Libbey & Company Ltd.; 2001. p. 233–9.
87. Kieboom BC, Kiefte-de Jong JC, Eijgelsheim M, Franco OH, Kuipers EJ, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. *Am J Kidney Dis* 2015;66(5):775–82.
88. Shils M. Magnesium. In: Shils M, Olson J, Shike M, Ross A, editors. *Modern nutrition in health and disease*. Baltimore (MD): Williams & Wilkins; 1999. p. 169–92.
89. Larsson SC. Urinary magnesium excretion as a marker of heart disease risk. *Am J Clin Nutr* 2013;97:1159–60.
90. Joosten MM, Gansevoort RT, Mukamal KJ, Kootstra-Ros JE, Feskens EJM, Geleijnse JM, Navis G, Bakker SJL. Urinary magnesium excretion and risk of hypertension: the prevention of renal and vascular end-stage disease study. *Hypertension* 2013;61:1161–7.
91. Rude RK. Magnesium metabolism and deficiency. *Endocrinol Metab Clin North Am* 1993;22:377–95.

92. Rubin H. Central roles of Mg<sup>2+</sup> and MgATP<sup>2-</sup> in the regulation of protein synthesis and cell proliferation: significance for neoplastic transformation. *Adv Cancer Res* 2005;93:1–58.
93. Pantin CFA. On the physiology of amoeboid movement. IV. The action of magnesium. *Br J Exp Biol* 1925–26;3:297–312.
94. Resnick LM. Cellular calcium and magnesium metabolism in the pathophysiology and treatment of hypertension and related metabolic disorders. *Am J Med* 1992;93:11S–20S.
95. Resnick LM. Cellular ions in hypertension, insulin resistance, obesity, and diabetes: a unifying theme. *J Am Soc Nephrol* 1992;3:578–85.
96. Resnick LM. Ionic basis of hypertension, insulin resistance, vascular disease, and related disorders: the mechanism of “syndrome X”. *Am J Hypertens* 1993;6:123S–34S.
97. Seelig MS. The requirement of magnesium by the normal adult. *Am J Clin Nutr* 1964;14:242–90.
98. Seelig MS. Human requirements of magnesium; factors that increase needs. In: Durlach J, ed. *1er Symposium International sur le Deficit Magnesique en Pathologie Humaine [First International Symposium on Magnesium Deficiency in Human Pathology]*. Vittel: SGEMV, 1971:11–38 (in French).
99. Hunt CD, Johnson LK. Magnesium requirements: new estimations for men and women by cross-sectional statistical analyses of metabolic magnesium balance data. *Am J Clin Nutr* 2006;84:843–52.
100. Amiot D, Hioco D, Durlach J. Frequence du deficit magnesique chez le sujet normal et dans diverses osteopathies. [Frequency of magnesium deficit in the normal subjects and in various steopathies]. *J Med Besancon* 1969;5:371–8 (in French).
101. Clarkson EM, Warren RL, McDonald SJ, de Wardener HE. The effect of a high intake of calcium on magnesium metabolism in normal subjects and patients with chronic renal failure. *Clin Sci* 1967;32:11–8.
102. Sojka J, Wastney M, Abrams S, Lewis SF, Martin B, Weaver C, Peacock M. Magnesium kinetics in adolescent girls determined using stable isotopes: effects of high and low calcium intake. *Am J Physiol* 1997;273:R710–5.
103. Green JH, Booth C, Bunning R. Impact of supplementary high calcium milk with additional magnesium on parathyroid hormone and biochemical markers of bone turnover in postmenopausal women. *Asia Pac J Clin Nutr* 2002;11:268–73.
104. Domrongkitchaiporn S, Ongphiphadhanakul B, Stithantrakul W, Piasu N, Chansirikam S, Puavilai G, Rajatanavin R. Risk of calcium oxalate nephrolithiasis after calcium or combined calcium and calcitriol supplementation in postmenopausal women. *Osteoporos Int* 2000;11:486–92.
105. Kärkkäinen MU, Wiersma JW, Lamberg-Allardt CJ. Postprandial parathyroid hormone response to four calcium-rich foodstuffs. *Am J Clin Nutr* 1997;65:1726–30.
106. Doyle L, Flynn A, Cashman K. The effect of magnesium supplementation on biochemical markers of bone metabolism or blood pressure in healthy young adult females. *Eur J Clin Nutr* 1999;53:255–61.
107. Basso LE, Ubbink JB, Delpont R, Spies J, Vermaak WJ. Effect of magnesium supplementation on the fractional intestinal absorption of <sup>45</sup>CaCl<sub>2</sub> in women with a low erythrocyte magnesium concentration. *Metabolism* 2000;49:1092–6.
108. Kato Y, Yamaguchi S, Yachiku S, Nakazono S, Hori J, Wada N, Hou K. Changes in urinary parameters after oral administration of potassium-sodium citrate and magnesium oxide to prevent urolithiasis. *Urology* 2004;63:7–11; discussion: 2.
109. Sei M, Nakamura H, Miyoshi T. Nutritional epidemiological study on mineral intake and mortality from cardiovascular disease. *Tokushima J Exp Med* 1993;40:199–207.
110. Burnett-Hartman AN, Fitzpatrick AL, Gao K, Jackson SA, Schreiner PJ. Supplement use contributes to meeting recommended dietary intakes for calcium, magnesium, and vitamin C in four ethnicities of middle-aged and older Americans: the Multi-Ethnic Study of Atherosclerosis. *J Am Diet Assoc* 2009;109:422–9.
111. Durlach J. Recommended dietary amounts of magnesium: Mg RDA. *Magnes Res* 1989;2:195–203.
112. Dai Q, Sandler R, Barry E, Summers R, Grau M, Baron J. Calcium, magnesium, and colorectal cancer. *Epidemiology* 2012;23:504–5.
113. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. *Atherosclerosis Risk in Communities Study*. *J Clin Epidemiol* 1995;48:927.
114. Dai Q, Shu XO, Deng X, Xiang YB, Li H, Yang G, Shrubsole MJ, Ji B, Cai H, Chow WH, et al. Modifying effect of calcium/magnesium intake ratio and mortality: a population-based cohort study. *BMJ Open* 2013;3:e002111.
115. Chiuev SE, Korngold EC, Januzzi JL Jr., Gantzer ML, Albert CM. Plasma and dietary magnesium and risk of sudden cardiac death in women. *Am J Clin Nutr* 2011;93:253–60.
116. Zhang W, Iso H, Ohira T, Date C, Tamakoshi A. Associations of dietary magnesium intake with mortality from cardiovascular disease: the JACC study. *Atherosclerosis* 2012;221(2):587–95.
117. Lutsey PL, Alonso A, Michos ED, Loehr LR, Astor BC, Coresh J, Folsom AR. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2014;100:756–64.
118. Moore-Schiltz L, Albert JM, Singer ME, Swain J, Nock NL. Dietary intake of calcium and magnesium and the metabolic syndrome in the National Health and Nutrition Examination (NHANES) 2001–2010 data. *Br J Nutr* 2015;14(6):1–12.
119. Rosanoff A. Rising Ca:Mg intake ratio from food in USA Adults: a concern? *Magnes Res* 2010;23:S181–93.
120. Carpenter TO. Disturbances of vitamin D metabolism and action during clinical and experimental magnesium deficiency. *Magnes Res* 1988;1:131–9.
121. Medalle R, Waterhouse C, Hahn TJ. Vitamin D resistance in magnesium deficiency. *Am J Clin Nutr* 1976;29:854–8.
122. Rösler A, Rabinowitz D. Magnesium-induced reversal of vitamin-D resistance in hypoparathyroidism. *Lancet* 1973;1:803–4.
123. Rude RK, Adams JS, Ryzen E, Endres DB, Niimi H, Horst RL, Haddad JG Jr., Singer FR. Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency. *J Clin Endocrinol Metab* 1985;61:933–40.
124. Seelig MS. Vitamin D and cardiovascular, renal, and brain damage in infancy and childhood. *Ann N Y Acad Sci* 1969;147:539–82.
125. Seelig MS. Vitamin D—risk vs benefit. *J Am Coll Nutr* 1983;2:109–10.
126. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116:2062–72.
127. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2012;95:91–100.
128. Schöttker B, Haug U, Schomburg L, Kohrle J, Perna L, Müller H, Holleczek B, Brenner H. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. *Am J Clin Nutr* 2013;97:782–93.
129. Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008;168:1629–37.
130. Pittas AG, Nelson J, Mitri J, Hillmann W, Garganta C, Nathan DM, Hu FB, Dawson-Hughes B; Diabetes Prevention Program Research Group. Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. *Diabetes Care* 2012;35:565–73.
131. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr* 2011;65:1005–15.
132. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007;92:2017–29.
133. Sun Q, Shi L, Rimm EB, Giovannucci EL, Hu FB, Manson JE, Rexrode KM. Vitamin D intake and risk of cardiovascular disease in US men and women. *Am J Clin Nutr* 2011;94:534–42.
134. Leu M, Giovannucci E. Vitamin D: epidemiology of cardiovascular risks and events. *Best Pract Res Clin Endocrinol Metab* 2011;25:633–46.

135. Giovannucci E. Epidemiological evidence for vitamin D and colorectal cancer. *J Bone Miner Res* 2007;22(Suppl 2):V81–5.
136. Lee JE, Li H, Chan AT, Hollis BW, Lee IM, Stampfer MJ, Wu K, Giovannucci E, Ma J. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. *Cancer Prev Res (Phila)* 2011;4:735–43.
137. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26, 335 cases from 60 observational studies. *Nutr Cancer* 2009;61:47–69.
138. Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer—ready for prime time? *N Engl J Med* 2011;364:1385–7.
139. Shapses SA, Manson JE. Vitamin D and prevention of cardiovascular disease and diabetes: why the evidence falls short. *JAMA* 2011;305:2565–6.
140. Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level: implications for meta-analyses and setting vitamin D guidelines. *Dermatoendocrinol* 2011;3:199–204.
141. Grant WB. Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyvitamin D and all-cause mortality rate. *Dermatoendocrinol* 2012;4:198–202.
142. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, et al. The VITamin D and Omega-3 Trial (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 2012;33:159–71.
143. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. *Am J Clin Nutr* 2008;88:1519–27.
144. International Agency for Research on Cancer. Vitamin D and cancer—a report of the IARC working group on vitamin D. Lyon (France): World Health Organization Press; 2008.
145. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. *Anticancer Res* 2011;31:607–11.
146. Reddy V, Sivakumar B. Magnesium-dependent vitamin-D-resistant rickets. *Lancet* 1974;1:963–5.
147. Risco F, Traba ML. Influence of magnesium on the in vitro synthesis of 24,25-dihydroxyvitamin D<sub>3</sub> and 1 alpha, 25-dihydroxyvitamin D<sub>3</sub>. *Magnes Res* 1992;5:5–14.
148. Risco F, Traba ML. Possible involvement of a magnesium dependent mitochondrial alkaline phosphatase in the regulation of the 25-hydroxyvitamin D<sub>3</sub>-1 alpha-and 25-hydroxyvitamin D<sub>3</sub>-24R-hydroxylases in LLC-PK1 cells. *Magnes Res* 1994;7:169–78.
149. Fuss M, Bergmann P, Bergans A, Bagon J, Cogan E, Pepersack T, Van Gossom M, Corvilain J. Correction of low circulating levels of 1,25-dihydroxyvitamin D by 25-hydroxyvitamin D during reversal of hypomagnesaemia. *Clin Endocrinol (Oxf)* 1989;31:31–8.
150. Deng X, Song Y, Manson JE, Signorello LB, Zhang SM, Shrubsole MJ, Ness RM, Seidner DL, Dai Q. Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. *BMC Med* 2013;11:187.
151. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–8.
152. Song Y, Manson JE, Cook NR, Albert CM, Buring JE, Liu S. Dietary magnesium intake and risk of cardiovascular disease among women. *Am J Cardiol* 2005;96:1135–41.
153. Wark PA, Lau R, Norat T, Kampman E. Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis. *Am J Clin Nutr* 2012;96:622–31.
154. Qu X, Jin F, Hao Y, Zhu Z, Li H, Tang T, Dai K. Nonlinear association between magnesium intake and the risk of colorectal cancer. *Eur J Gastroenterol Hepatol* 2013;25:309–18.
155. Chu HI, Liu SH, Hsu HC, Choa HC, Cheu SH. Calcium, phosphorus, nitrogen, and magnesium metabolism in normal young Chinese adults. *Chin Med J* 1941;59:1–33.